Adaptive basal phosphorylation of eIF2alpha is responsible for resistance to cellular stress-induced cell death in Pten-null hepatocytes.

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Public Summary:
Cellular adaptation to environmental stress is a major mechanism for tumor cells to respond to its stressful environment. The molecular mechanismfor such response is not understood. Our study provided a novel molecular mechanism on how activation of PI3K/AKT signaling may allow cells to deal with the stress conditions and ultimately adapt to and survive the new environment. This adaptive response of the Pten-null hepatocytes to oxidative (and other) stress may allow them to survive the stressful environment of fatty liver in vivo and play a role in the development of tumors. Our study uncovered a novel role of PTEN in regulating the adaptive response of cancer cells to chronic stress through modulating the CReP/eIF2a pathway.

Scientific Abstract:
The alpha-subunit of eukaryotic initiation factor 2 (eIF2alpha) is a key translation regulator that plays an important role in cellular stress responses. In the present study, we investigated how eIF2alpha phosphorylation can be regulated by a tumor suppressor PTEN (phosphatase and tensin homolog deleted on chromosome 10) and how such regulation is used by PTEN-deficient hepatocytes to adapt and cope with oxidative stress. We found that eIF2alpha was hyperphosphorylated when Pten was deleted, and this process was AKT dependent. Consistent with this finding, we found that the Pten-null cells developed resistance to oxidative glutamate and H(2)O(2)-induced cellular toxicity. We showed that the messenger level of CReP (constitutive repressor of eIF2alpha phosphorylation), a constitutive phosphatase of eIF2alpha, was downregulated in Pten-null hepatocytes, providing a possible mechanism through which PTEN/AKT pathway regulates eIF2alpha phosphorylation. Ectopic expression of CReP restored the sensitivity of the Pten mutant hepatocytes to oxidative stress, confirming the functional significance of the downregulated CReP and upregulated phospho-eIF2alpha in the resistance of Pten mutant hepatocytes to cellular stress. In summary, our study suggested a novel role of PTEN in regulating stress response through modulating the CReP/eIF2alpha pathway.

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